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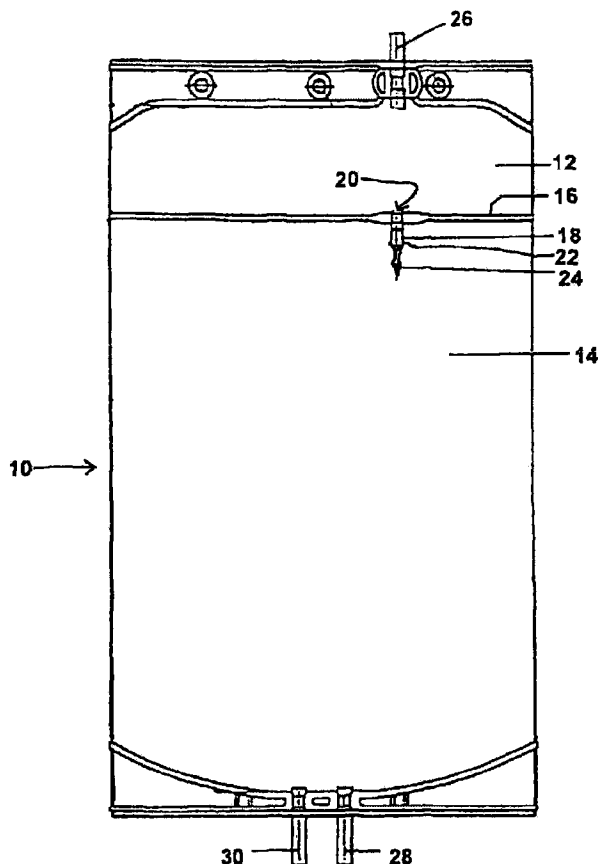
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(54) Title: **MULTIPLE COMPARTMENT BAG ASSEMBLY FOR DIALYSIS FLUID**



(57) Abstract: The invention concerns a multiple compartment flexible bag assembly including a first predetermined volume of an aqueous sodium bicarbonate component solution contained in at least one of the multiple compartments and a second predetermined volume of an aqueous acid component solution contained in at least another of the multiple compartments, the component solutions being intended to be mixed together to obtain a peritoneal dialysis, hemodialysis or replacement fluid, characterized in that the aqueous acid component solution comprises an amount of dissolved carbon dioxide. The partial pressure value of carbon dioxide exhibited the aqueous acid component solution is preferably matched with the partial pressure value of carbon dioxide determined for the aqueous sodium bicarbonate component solution.



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Multiple compartment bag assembly for dialysis fluid

5 This invention relates to peritoneal dialysis, hemodialysis and replacement fluids. More particularly, the invention relates to a dialysis or replacement fluid separated into two or more component solutions intended for admixture preliminary to use. Admixture of the component solutions provides the final dialysis or replacement fluid.

10 BACKGROUND OF THE INVENTION

With the advent of bicarbonate, in general sodium bicarbonate, being the preferred buffer and indeed natural buffer as compared to acetates or lactates, dialysis and replacement fluids preferably
15 comprise bicarbonate. Dialysis and replacement fluids comprising bicarbonate anions in general need to be provided in the form of at least two separate component solutions, one comprising essentially only the bicarbonate component and the other comprising the so-called minor electrolytes including Ca^{++} , Mg^{++} and K^+ cations, and
20 Na^+ . In some cases, a Na^+ -content, additional to that provided by NaHCO_3 , may conveniently be provided together with the bicarbonate component.

The need for separation of the bicarbonate component from
25 other components which may comprise Ca^{++} and Mg^{++} cations is that the required amounts of these cations, in particular Ca^{++} , cannot be stored together with bicarbonate for any appreciable period of time without precipitation of Ca^{++} and Mg^{++} carbonates. However, if the bicarbonate and Ca^{++} and Mg^{++} component solutions are mixed
30 together shortly before use of the mixture as a dialysis or replacement fluid, precipitation does not occur within a time which is adequate for the mixture to be employed for its intended purpose.

One of the difficulties encountered with bicarbonate solutions i.e. in this case the bicarbonate component solution, is that such solutions are inclined to lose CO_2 and form carbonates, which leads to an increased pH. There are suggestions, such as provided in USP 5211 643, that it is of importance that the pH of bicarbonate solutions should be below 7.6 if formation of calcium carbonate seeds is to be avoided when mixing of the bicarbonate solution and Ca^{++} - containing solution takes place, which in turn encourages further CaCO_3 precipitation. On the other hand, there are alternative suggestions, as represented by PCT/US00/20486 (WO 01/17534 A1) that a low pH of less than 7.6 is not critical and indeed a pH of 8.6 to 10 is indicated to be an acceptable pH range for the bicarbonate solution. In this PCT publication, it is furthermore indicated that the need for a gas-impermeable over-wrap limiting migration or escape of CO_2 from the bicarbonate solution can be dispensed with. In other words, no harm is seen in allowing CO_2 to escape from the bicarbonate solution and for the attendant pH to increase to a value of from 8.6 up to even 10, suggesting a higher concentration of CO_3^{--} ions.

The present invention is concerned with advantageous alternatives to both of the approaches discussed above. Thus, in the case of USP 5, 211, 643, the need for the bicarbonate solution to be possessed of a pH below 7.6 is critical to the invention there described. Products involving sodium bicarbonate solutions having a pH in excess of 7.6, for example 7.8 or even up to 8.8, however, have not demonstrated difficulties arising from calcium carbonate precipitation when mixed with Ca^{++} -containing solutions, provided that the mixtures are employed for their intended purpose within a reasonable period of time, such as within 24 hours from the time that the component solutions are mixed. On the other hand, it is known that bicarbonate-containing solutions contained in flexible plastic material bags are inclined to lose CO_2 and for the pH of the solution to thereby reach higher pH values. More particularly, it is of importance that the final mixture of the alkaline bicarbonate solution

with the Ca^{++} -containing solution which is generally an acid solution, usually comprising both Ca^{++} and Mg^{++} cations, be within a physiologically acceptable pH range of about 7.2 to 7.3. It is accordingly of importance to gain proper control over the extent of CO_2 migration from bicarbonate solutions. One mode of gaining some control involves use of gas-impermeable over-wrap material over-wrapping flexible plastic bags each separately containing the components of the desired mixture of bicarbonate and acid solutions. One practical difficulty with this procedure is that the over-wrap material, also in the form of a flexible bag, is normally evacuated of air so that the over-wrap material seats over the surfaces of plastic material containing the bicarbonate and other solutions. This evacuation procedure inevitably leads to creases in the over-wrap material forming pockets into which CO_2 gas may escape through the plastic material container from the bicarbonate solution. Since the volume occupied by the over-wrap material is necessarily greater than the volume of the flexible bag containers containing the bicarbonate and other solutions, there is always a volume within the over-wrap material which can receive CO_2 gas escaping from the bicarbonate solution.

Escape of carbon dioxide from the sodium bicarbonate component solution may be limited by means of gas-impermeable over-wrap film material enclosing the flexible bag assembly. Over-wrap film materials having gas-impermeable characteristics include polypropylene-polyvinyl alcohol copolymers which however need to be employed in their over-wrap role subsequent to sterilization of the filled flexible bag assembly if the gas-impermeable characteristics thereof are to be retained.

Film materials employed for producing the multi-compartment flexible bag assembly might be of PVC or non-PVC type. Such materials as are presently available are however invariably permeable to carbon dioxide gas to varying degrees. Such permeation of carbon

dioxide from the sodium bicarbonate component solution leads to an increase in sodium carbonate content and hence to increased pH levels. Furthermore, loss of carbon dioxide leads to a lowering of the desired content or availability of bicarbonate ions in the final admixed composition of the sodium bicarbonate component solution and the acid component solution. The escape of carbon dioxide is thus to be avoided or controlled as best as is possible.

The present invention is more particularly directed to achieving improved control and limitation of the amounts of CO₂ gas which can escape from bicarbonate-containing solutions into gas-impermeable over-wrap material enclosing bicarbonate-containing and other solutions. The improved control and limitation of the amounts of CO₂ gas which can escape or does escape from bicarbonate-containing solutions may also provide opportunities for eliminating the need for an over-wrap. An additional associated consideration is related to influences on one another of partial pressures of CO₂ of different solutions to be mixed together to obtain final peritoneal dialysis, hemodialysis and replacement fluids. The invention accordingly involves evaluations of the partial pressure of CO₂ of bicarbonate-containing solutions and other solutions with which the bicarbonate-containing solutions are to be mixed.

SUMMARY OF THE INVENTION

The invention provides a multiple compartment flexible bag assembly including a first predetermined volume of an aqueous sodium bicarbonate component solution contained in at least one of the multiple compartments and a second predetermined volume of an aqueous acid component solution contained in at least another of the multiple compartments, characterized in that the aqueous acid component solution comprises an amount of dissolved carbon dioxide.

Particular advantages of comprising an amount of carbon dioxide in the aqueous acid component solution include the fact that firstly an amount of carbon dioxide is available in this aqueous acid component solution so that, upon mixing of the bicarbonate component solution with the acid component solution, the bicarbonate solution is exposed to an environment of a CO_2 - containing solution rather than a CO_2 - free solution, and secondly that such amount of carbon dioxide which migrates across the packaging material from the acid component solution into a gas-impermeable over-wrap flexible bag will limit by a corresponding amount the amount of carbon dioxide which can migrate from the sodium bicarbonate component solution into said over-wrap flexible bag. On the other hand, embodiments of the multiple compartment flexible bag assembly of the invention which do not comprise a gas-impermeable over-wrap flexible bag may share the characteristic of the invention in that such embodiments may similarly avoid that bicarbonate solutions become exposed to a CO_2 -free environment upon mixing with the acid component solution.

The amount of dissolved carbon dioxide in the aqueous acid component solution may be that amount which is dissolved in the acid component solution following on bubbling and distributing CO_2 gas into the bottom of a tank containing the aqueous acid component solution. Preferably, the acid component solution is maintained at a temperature of about 25°C under atmospheric conditions during this procedure.

The amount of carbon dioxide dissolved in the aqueous acid component solution is most preferably that amount which leads to a partial pressure value for CO_2 (pCO_2) in the aqueous acid component solution which approximates or equates with the pCO_2 value in the bicarbonate component solution. Thus, for example, if the total CO_2 , HCO_3^- , and CO_3^{--} content (hereinafter TCO_2) of the bicarbonate solution is about 700 mmol/l and the bicarbonate component solution is to be provided in the preferable pH range of 7.8 to 8.0, the pCO_2

value of this solution is between about 220 and 290 mmHg at a temperature of about 20-25° C and pressure of about 760 mm Hg. This means that from about 8 mmol/l to about 11 mmol/l of CO₂ should most preferably be dissolved in the aqueous acid component solution. Further more detailed explanations are provided below, with reference to an exemplary graphical representation, showing inter-relationships between pCO₂, pH, log [CO₂aq], log [HCO₃⁻] and log [CO₃²⁻].

10 In accordance with the invention, it has furthermore been determined that, for hemodialysis and replacement solutions prepared by mixing of the bicarbonate component solution and the acid component solution, in order to achieve the desired final HCO₃⁻ concentration of 30 to 40 mmol/l, preferably 36 mmol/l and at the same time also to achieve the preferred substantial matching of the pCO₂ values for the bicarbonate and acid component solutions, the pH of the bicarbonate component solution should preferably be increased by the addition of an alkaline-acting substance other than NaHCO₃ alone. The alkaline acting substance is most preferably Na₂CO₃ since CO₃²⁻ is one of the anion entrants comprised in the above-mentioned "TCO₂" total. However, the alkaline-acting substance may for example be NaOH, and/or a small amount of KOH replacing such amount of K⁺ as may be required which is generally made available in the acid component solution. In this fashion, it is possible to establish specific predetermined pCO₂ values in bicarbonate-containing solutions, which values may be selected dependently of available flexible bag materials and the nature of the acid component solution or other solutions with which the bicarbonate component solution is to be mixed.

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As will be more apparent from further disclosure below, the increase of the pH of the acid component solution caused by mixing with the alkaline bicarbonate component solution leads dissolved CO₂ to convert to carbonic acid or rather H⁺ and HCO₃⁻ ions, the H⁺ or

protons then being available to either convert CO_3^{--} ions to HCO_3^- ions or lower the pH of the mixed component solution. Any such increase in content of HCO_3^- ions of course needs to be taken into account in the process of securing the correct and desirable concentration of HCO_3^- ions in the final mixed component solution.

Formulations of acid component solutions of the invention for the preparation of hemodialysis (and replacement) (HD) fluids and peritoneal dialysis (PD) fluids are as follows:

	HD	PD	
Sodium	0-4000	0-400	mmol/l
Potassium	0-1000	0-5	mmol/l
Calcium	0-50	0-17.5	mmol/l
Magnesium	0-30	0-7.5	mmol/l
Chloride	0-5500	0-500	mmol/l
Glucose	0-2000	0-3000	mmol/l
Acid	0-100	0-100	mmol/l
Dissolved CO_2	0.5-30	0.5-30	mmol/l
pH	2-5	2-5	
pCO_2	10-675	10-760	mmHg
Water			

Preferably, the amount of dissolved CO_2 in the above solutions is within the range of 5 to 15 mmol/l leading to a pCO_2 value within the range of 110 to 350 mmHg at a pH of 2 to 4.3.

Exemplary acids which may be employed in the acid component solution include hydrochloric acid, acetic acid, lactic acid and of course the carbonic acid formed by the CO_2 dissolved in the aqueous medium when the pH of the solution is increased. Preferably, the amount of the acid (excluding carbonic acid) in the acid component solution is from 1-10 mmol/l for a dilute form and from 40-100 mmol/l for a concentrated form. Formulations of the acid component solution

may furthermore comprise additional substances such as a citrate, fumarate, malate or succinate, either in the form of an acid or a salt thereof.

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EXAMPLES

More specific Examples of formulations of acid component solutions of the invention for the preparation of HD fluids are set forth below:

10

Example 1 (dilute form HD)

	Calcium chloride. 2 H ₂ O	0,271 g	(1.84 mmol/l)
	Sodium chloride	6,450 g	(110 mmol/l)
15	Lactic acid	0.284 g	(3.16 mmol/l)
	Magnesium chloride. 6 H ₂ O	0.108 g	(0.53 mmol/l)
	Dissolved CO ₂	5-30mmol/l	
	pH	3.1	
	pCO ₂	150-750 mmHg	
20	Water to volume	1000 ml	

Example 2 (concentrated form HD, including glucose)

	Calcium chloride. 2H ₂ O	5.145 g	(34.8 mmol/l)
25	Magnesium chloride. 6 H ₂ O	2.033 g	(10 mmol/l)
	Glucose anhydrous	22.00 g	(22 mmol/l)
	Lactic acid	5.40 g	(60 mmol/l)
	Dissolved CO ₂	5-30 mmol/l	
	pH	2.3	
30	pCO ₂	150-750 mmHg	
	Water to volume	1000 ml	

Preferably, as already mentioned above, the amount of dissolved CO₂ in the above solutions is within the range of 5 to 15 mmol/l leading to a pCO₂ value within the range of 110 to 350 mmHg.

5 A more specific Example of a formulation of an acid component solutions of the invention suitable for the preparation of PD fluids is set forth below:

Example 3 (PD form)

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Sodium chloride	5.30 g	(91 mmol/l)
Calcium chloride. 2H ₂ O	4.77 g	(32.2 mmol/l)
Magnesium chloride. 6H ₂ O	1.62 g	(8.0 mmol/l)
Glucose anhydrous	500 g	(2780 mmol/l)
15 Acid (HCl)		0.2 – 0.4 mmol/l
Dissolved CO ₂		5-30 mmol/l
pH		3.2
pCO ₂		110-675 mmHg
Water to volume		1000 ml

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As mentioned, the partial pressure of CO₂ exhibited by the aqueous acid component solution most preferably substantially matches that of the aqueous bicarbonate component solution. The invention accordingly also provides a process for preparing an aqueous acid component solution, which may be of the particular formulations described above, which comprises the steps of determining the carbon dioxide partial pressure value exhibited by an aqueous bicarbonate component solution, preparing the aqueous acid component solution, and introducing carbon dioxide into the prepared aqueous acid component solution to obtain an aqueous acid component solution which exhibits a carbon dioxide partial pressure value which substantially matches said carbon dioxide partial pressure value determined for said aqueous bicarbonate component solution. The dissolved carbon dioxide thus provides a source of

protons contributing to a lowering of the pH upon admixture of a sodium bicarbonate component solution with the acid aqueous acid component solution. The pH of the sodium bicarbonate component solution may be as high as about 9.5, but is preferably less than about 8.5 at the time that admixture thereof with the acid component solution takes place. The pH of the acid component solution, may be between about 1.5 and 5, but in compositions of acid component solutions comprising glucose, the pH should most preferably be between about 3.0 and 3.4, preferably about 3.2, during sterilization processes.

A further major advantage of including carbon dioxide in the acid component solution is that the weak acid properties of carbonic acid (formed by dissolved carbon dioxide when increasing pH) enables a higher pH value to be provided in the acid component solution as compared to employing only a relatively strong acid, such as lactic acid or hydrochloric acid, for purposes of providing a source of protons depressing carbonate content by conversion to bicarbonate and lowering the pH of the sodium bicarbonate component solution when this is admixed with the acid component solution. The inclusion of carbon dioxide in the acid component solution is of particular advantage where the acid component solution also comprises amounts of glucose, such as described above, since glucose degradation products are formed during autoclaving or other sterilization processes not only at high pH but also when the pH is too low (below about 3.2). The carbon dioxide dissolved in the acid component solution provides availability of a proportion of protons required for lowering the pH of the admixed solutions while at the same time contributing to avoiding an unacceptably low pH for glucose-containing acid component solutions during sterilization processes.

The sodium bicarbonate component solution, in a fashion similar to the acid component solution may optionally also comprise

dissolved carbon dioxide. Exemplary sodium bicarbonate component solutions comprise from about 10 mmol/l to 1100 mmol/l sodium bicarbonate.

5 Thus, for example, a sodium bicarbonate component solution suitable for use as a component of a renal intensive care substitution fluid may comprise 58.8 g/l or 700 mmol/l of sodium bicarbonate. This type of solution may initially be comprised in a tank and carbon dioxide bubbled and distributed into the bottom of the tank so that the
10 solution becomes essentially saturated with carbon dioxide. The temperature of the solution during the time that carbon dioxide is introduced is preferably about 25°C, at the prevailing atmospheric pressure, as in the case of the acid component solution. The pH of the bicarbonate solution may be lowered to a pH of about 7.3 or even
15 as low as 6.0 if the bicarbonate concentration is lowered, as will be apparent from the following description with reference to the accompanying drawings.

20 A first predetermined volume of the bicarbonate component solution is introduced into one of the compartments of the multiple compartment flexible bag assembly and a second predetermined volume of other component solutions is introduced into other of the separate compartments and the filled assembly is then subjected to heat sterilization, preferably steam-sterilization at about 120°C. CO₂
25 gas is caused to escape from the bicarbonate component solution so that the pH of this solution advantageously reaches a value of at least 6.8. Preferably, however, for stability and storage reasons, the pH of the bicarbonate component solution is allowed to rise to a pH value of between about 7.8 and 8.0 because at elevated pH values the pCO₂
30 values in the bicarbonate component solution are significantly lower than at lower pH values. Thus, the tendency for CO₂ to migrate across the walls of the packaging material is reduced and the stability of the bicarbonate solution is increased substantially.

Exemplary formulations of sodium bicarbonate component solutions suitable for the preparation of HD fluids, after steam-sterilization, are as follows:

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Example 4 (concentrated form HD)

10	Sodium bicarbonate	58.8 g	(700 mmol/l)
	Water to volume	1000 ml	
	Min. conc. CO ₂	11 mmol/l	
	Max. conc. with added CO ₂	30 mmol/l	
	pH (at min. CO ₂)	7.8	
15	pH (with added CO ₂)	7.4	
	pCO ₂ (at min. CO ₂)	300 mmHg	
	pCO ₂ (at max. CO ₂)	760 mmHg	

20 **Example 5 (dilute form HD, including K⁺)**

	Sodium chloride	6.450 g	(110 mmol/l)
	Sodium bicarbonate	3.090g	(36.8mmol/l)
	Potassium chloride	0.157 g or 0.314 g	(2 mmol/l or 4 mmol/l)
25	Water to volume	1000 ml	
	Min. conc. CO ₂	0.5 mmol/l	
	Max. conc. (with added CO ₂)	33 mmol/l	
	pH (at min. CO ₂)	7.9	
	pH (with added CO ₂)	6.2	
30	pCO ₂ (at min. CO ₂)	11 mmHg	
	pCO ₂ (at max. CO ₂)	760 mmHg	

Example 6 (concentrated form HD)

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	Sodium bicarbonate	42 g	(500 mmol/l)
	Sodium carbonate	44 g	(415 mmol/l)

Water to volume	1000 ml
CO ₂ conc.	0.28 mmol/l
pH	9.3
pCO ₂	11 mmHg

5

An exemplary formulation of a sodium bicarbonate component solution suitable for preparation of PD fluids is set forth below:

Example 7 (PD form)

10

Sodium chloride	7.77 g	(134 mmol/l)
Sodium bicarbonate	0.882 g	(10.5 mmol/l)
Sodium lactate	3.54 g	(31.6 mmol/l)
CO ₂ conc.	4 mmol/l	

15

Water to volume	1000 ml
pH	6.5
pCO ₂	90 mmHg

20

A first predetermined volume of the above Example 4 sodium bicarbonate component concentrated form solution is to be related to, i.e. admixed, with a second predetermined volume of the above Example 1 of acid component dilute form solution to obtain a final HD (or replacement) fluid. The total unit volume of the final HD fluid is conveniently selected to be 5 l. Thus, a first predetermined volume of said sodium bicarbonate solution would be 0.25 l to be admixed with a second predetermined volume of 4.75 l of said first formulation of acid component solution to provide 5 l of final HD or replacement fluid having the following composition:

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Calcium	1.75 mmol/l
Magnesium	0.5 mmol/l
Sodium	140 mmol/l
Chloride	109 mmol/l
Lactate	3.0 mmol/l

Bicarbonate	32.0 mmol/l
pH	7.0 – 7.4

Thus, in the above embodiment 0.25 l of the sodium bicarbonate component concentrated form solution would be contained in one compartment of a multiple compartment flexible bag assembly and 4.75 l of the acid component dilute form solution would be contained in another of the multiple compartments.

Similarly and conversely, a first predetermined volume of the above Example 5 sodium bicarbonate component dilute form solution (including potassium) is to be related to, i.e. – admixed, with a second predetermined volume of the above Example 2 acid component concentrated form solution to obtain a final HD (or replacement) fluid. The total unit volume of the final HD fluid is conveniently once again selected to be 5 l, in which case 4.75 l of said sodium bicarbonate component dilute form solution would be mixed with 0.25 l of said acid component concentrated form solution (including glucose) to obtain a final HD fluid having the following composition:

Calcium	1.75 mmol/l
Magnesium	0.5 mmol/l
Sodium	140 mmol/l
Chloride	109 mmol/l
Lactate	3.0 mmol/l
Bicarbonate	32.0 mmol/l
Glucose	6.1 mmol/l
Potassium	2 or 4 mmol/l
pH	7.0 – 7.4

Thus, in the above embodiment 0.25 l of the acid component solution would be contained in one compartment of the multiple compartment flexible bag assembly and 4.75 l of the bicarbonate

component solution would be contained in another of the multiple compartments.

A first predetermined volume of the above Example 7 PD sodium bicarbonate component solution is to be related to, i.e. admixed, with a second predetermined volume of the formulation of the above Example 3 PD acid component solution to obtain a final PD fluid. In the case of PD fluids, the total unit volume selected is generally about 2 l. Thus, as is described in our earlier Patent Application PCT/SE98/02146, for example, the second predetermined volume of said PD acid component solution may be either 60 ml or 100 ml or 160 ml (100 ml plus 60 ml) of the PD acid component solution to be admixed with a first predetermined volume of 1900 ml of said PD sodium bicarbonate component solution, which selection of second predetermined volumes provides opportunity to obtain three different types of PD solution as follows:

	60 ml	100 ml	160 ml
Magnesium	0.25	0.40	0.62 mM
Calcium	1.0	1.6	2.5 mM
Sodium	131.8	131.0	129.9 mM
Chloride	92.5	94	96.2 mM
Bicarbonate	10.2	10.0	9.7 mM
Lactate	30.6	30.0	29.2 mM
pH	7.3	7.3	7.3

Thus, a first predetermined volume of 1900 ml of the PD sodium bicarbonate component solution would be contained in one of the compartments of the multiple compartment flexible bag assembly, and two separate second predetermined volumes of the PD acid component solution would be contained in two separate other compartments.

A process of the invention for preparing a multi-compartment flexible bag assembly including an amount of an aqueous sodium

bicarbonate component solution in at least one of the multi-compartments and an aqueous acid component solution in at least another of the multi-compartments, includes the steps of providing a multi-compartment flexible bag assembly, each compartment being dimensioned to receive a predetermined volume of a component solution, preparing the aqueous sodium bicarbonate component solution and the aqueous acid component solution, dissolving an amount of carbon dioxide in at least the aqueous acid component solution, introducing the prepared aqueous sodium bicarbonate component solution into at least one of the multi-compartments of the multi-compartment flexible bag assembly, introducing the carbon dioxide-containing aqueous acid component solution into another of the multi-compartments of the multi-compartment flexible bag assembly, and subjecting the filled multi-compartment assembly to a sterilization procedure. The sterilization procedure generally followed is steam-sterilization under pressure at 120° C, but other procedures such as heat-sterilization or γ -sterilization may be followed, dependently of such factors as the nature of the component solutions and the materials of the flexible bag assembly.

Subsequent to the sterilization procedure, where this is for example a heat or steam-sterilization procedure, the filled multi-compartment assembly is generally allowed to cool to room temperature, e.g. about 20°C. The filled multi-compartment assembly may, either before or after the sterilization procedure, dependent on the need or availability of materials, be over-wrapped with a gas-impermeable plastic material film or aluminum enclosure for purposes of retaining such amounts of carbon dioxide gas which may migrate across the walls of the flexible bag assembly from the bicarbonate and acid component solutions within the over-wrapping.

As already mentioned, additional to dissolving carbon dioxide gas in the aqueous acid component solution, it is preferable, in accordance with a process of the invention, also to dissolve carbon

dioxide gas in the prepared sodium bicarbonate solution. In this way, the pH of the sodium bicarbonate solution may be lowered by the weak acid effect of carbonic acid formed by the dissolution of carbon dioxide in the aqueous medium of the sodium bicarbonate solution.

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Regarding film materials employed for producing the multi-compartment flexible bag assembly, it is noted that some PVC materials may not be suited for containing solutions having a pH in excess of about 6.5. Thus, where a sodium bicarbonate solution is envisaged as one of the component solutions, as in the present invention, a specially adapted PVC able to withstand higher pH values should be employed. Exemplary of such a PVC material is one made available by Draka of Holland under the Trademark "Alka". It is understood that this PVC material comprises plasticiser or lubricant contents which are different from those of conventional PVC materials.

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Dialysis or replacement fluids of the invention may comprise an amount of glucose, for example 0 mmol/l to about 250 mmol/l in the final admixed solutions. The glucose component may be comprised in the carbonated acid component solution comprising the minor electrolytes. However, it is also possible and sometimes preferable to provide a third separate glucose component solution, separate of the bicarbonate and acid component solutions, which can be of advantage in that the pH of the glucose component solution can be set to the ideal pH value for heat or steam sterilization. Thus, it is most preferable that a glucose solution be at a pH of 3.2 ± 0.1 if the formation of glucose degradation products (GDP's) during sterilization are to be kept to a minimum. Similarly, it is preferable, although not essential at lower pH levels, to keep the glucose separate from the minor electrolytes, in particular Ca^{++} , during heat or steam sterilization processes.

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Exemplary sodium bicarbonate-containing solutions comprised in one compartment of the multi-compartment flexible bag assembly comprise from about 600 mmol/l, to 800 mmol/l of solution. The solution most preferably comprises an amount of dissolved CO₂ leading to formation of carbonic acid, or another acid such as hydrochloric acid or citric acid for purposes of lowering the pH of the bicarbonate solution to a pH value somewhat less than 8, preferably less than 7.4, so that after heat sterilization, during which an amount CO₂ is lost, the bicarbonate solution is at a pH which does not exceed about 8 and is preferably in the range of 7.8 to 7.9. This bicarbonate component solution, when mixed with the acid component solution and optionally a separate glucose-containing component solution, should provide a final solution for use as a dialysis liquid or replacement fluid which is possessed of a pH of 7.2 to 7.4, i.e. in the physiologically acceptable range.

Additional to dissolving CO₂ in both the bicarbonate component solution and the acid component solution, CO₂ may also be dissolved in a separately prepared glucose component solution which is to be filled into a separate compartment of the multi-compartment flexible bag assembly. This dissolved CO₂ can also contribute to limiting the loss of CO₂ from the sodium bicarbonate component solution, in the same fashion as does the CO₂ dissolved in the acid component solution.

BRIEF DESCRIPTION OF DRAWINGS

Exemplary multi-compartment flexible bag assemblies are shown in the accompanying drawings:

Figure 1 shows a dual-compartment flexible bag assembly;

Figure 2 shows a triple-compartment flexible bag assembly; and

Figure 3 shows a multi-compartment flexible bag assembly over-wrapped with a gas-impermeable over-wrap material.

5 The accompanying drawings also include graphical representations in which:

Figure 4 shows the relationship, by way of example, of the influence of pH on the partial pressure of CO_2 (pCO_2) on a sodium bicarbonate, optionally including an amount of sodium carbonate and CO_2 , but in
10 any event providing a total " TCO_2 " = to about 700 mmol/l, TCO_2 being $[\text{HCO}_3^-] + [\text{CO}_3^{--}] + [\text{CO}_{2\text{aq}}]$;

Figure 5 shows the pCO_2 values of various " TCO_2 " bicarbonate solutions (optionally comprising sodium carbonate and CO_2) as
15 influenced by the pH of the solution; and

Figure 6 shows the logarithmic inter-relationship of the concentrations of dissolved CO_2 ($\text{CO}_{2\text{aq}}$), HCO_3^- and CO_3^{--} for a TCO_2 solution = 40 mmol/l as influenced by pH. This figure also reflects the pCO_2 value
20 for this particular TCO_2 solution as influenced by pH.

DETAILED DESCRIPTION OF DRAWINGS

Referring to Figure 1 of the drawings, reference numeral 10 refers
25 generally to a two-compartment flexible bag assembly, one compartment being referred to by reference numeral 12 and the other by reference numeral 14. One of the compartments, i.e. either the compartment 12 or the compartment 14 may contain a first predetermined volume of an aqueous sodium bicarbonate solution and
30 the other compartment 14 or 12 may contain a second predetermined volume of an aqueous acid component solution. The compartments 12 and 14 are divided by a transverse seal 16. A communication conduit 18 is provided between the seal 16 which has an open end 20 opening into compartment 12 and a temporarily closed end 22 located in

compartment 14. The temporarily closed end 22 is closed by means of a frangible pin 24 which, when manually broken opens the communication conduit 18 to enable the aqueous solution contained in the compartment 12 to be introduced into the compartment 14 and thus mixed with the aqueous solution contained in the compartment 14. Reference numerals 26 and 28 refer to filling conduits for filling the compartments 12 and 14 with the predetermined volumes of aqueous solutions. Reference numeral 30 refers to an outlet conduit for connection to a fluid line leading to HD (or substitution) monitoring equipment (not shown) or to a PD cycler (not shown) for introducing or replacing PD fluid in to the peritoneal cavity of a patient undergoing treatment.

In Figure 2, the same reference numerals as in Figure 1 are employed to refer to the same structural aspects of a three-compartment flexible bag assembly 10. In Figure 2, two compartments 12a and 12b are provided to contain two different quantities of an aqueous acid component solution, e.g. 60 ml and 100 ml, as described in the disclosure above. Seals 16a and 16b, communication conduits 20a and 20b, filling conduits 26a and 26b and 28 serve the same functions as described in relation to Figure 1. Reference numeral 32 refers to a drug delivery conduit carrying a re-seal plug 34 enabling a drug component to be introduced into the compartment 14.

Figure 3 shows the two-compartment flexible bag assembly of Figure 1 enclosed within a gas-impermeable over-wrap 36. The over-wrap is shown in an evacuated condition, reference numerals 38 referring to creases which form in the over-wrap material following an evacuation. The flexible bag assembly of Figure 2 may be similarly enclosed in over-wrap 36.

Referring to Figures 4 and 5 inter-relationships between partial pressures of CO₂ and pH at various concentrations of sodium carbonate can be noted. A portion of the graphic shown for a

concentration of 700 mmol/l sodium bicarbonate in Figure 4 is included in Figure 5.

Now, referring to Figure 6, there is shown the logarithmic inter-relationships of concentrations of CO_3^{--} , HCO_3^- and CO_2 (aq), i.e. dissolved CO_2 , at pH values between 2 and 11. Also shown is the logarithmic inter-relationship of the CO_2 partial pressure to said logarithmic inter-relationships of concentrations between said pH values. When bearing in mind that the present invention provides dissolved CO_2 in the acid component solution and that it is preferable that the pCO_2 value for the acid component solution approximates that of the bicarbonate component solution, it may for example be noted from Figure 5 that a high concentration bicarbonate component solution (700 mmol/l) at the preferred pH of 7.8 to 8 exhibits a pCO_2 value of between about 280 and 180 mm Hg. respectively. Accordingly, in this case the acid component solution which may be at a pH of 2 to 4 should most preferably be treated with CO_2 so as also to exhibit a pCO_2 value within or resembling this range. Similarly, if the bicarbonate component solution is for example 40 mmol/l and the pH of this solution is once again to be within the preferable pH range of 7.8 to 8, the bicarbonate component solution would exhibit a pCO_2 value of between about 18 and 11 mm Hg.

What is claimed is:

1. A multiple compartment flexible bag assembly including a first predetermined volume of an aqueous sodium bicarbonate component solution contained in at least one of the multiple compartments and a second predetermined volume of an aqueous acid component solution contained in at least another of the multiple compartments, the component solutions being intended to be mixed together to obtain a peritoneal dialysis, hemodialysis or replacement fluid, characterized in that the aqueous acid component solution comprises an amount of dissolved carbon dioxide.
2. A multiple compartment flexible bag assembly according to claim 1, in which the concentration of carbon dioxide dissolved in the aqueous acid component solution is from 0.5 to 30 mmol/l.
3. A multiple compartment flexible bag assembly according to claim 2, in which the concentration of dissolved carbon dioxide is from 5 to 15 mmol/l.
4. A multiple compartment flexible bag assembly according to claim 1, in which the partial pressure value of carbon dioxide exhibited by said aqueous acid component solution substantially matches the partial pressure value of carbon dioxide exhibited by said aqueous sodium bicarbonate component solution.
5. A multiple compartment flexible bag assembly according to claim 1, in which said second predetermined volume of the aqueous acid component solution is intended for admixture with said first predetermined volume of the bicarbonate component solution in the preparation of a hemodialysis or substitution fluid and in which the formulation of said aqueous acid component solution comprises the following

electrolytes, glucose, acid and dissolved carbon dioxide at the limits or within the range of concentrations, pH and pCO₂ values as follows:

5

Sodium	0 to 4000	mmol/l
Potassium	0 to 1000	mmol/l
Calcium	0 to 50	mmol/l
Magnesium	0 to 30	mmol/l
Chloride	0 to 5500	mmol/l
Glucose	0 to 2000	mmol/l
Acid	0 to 100	mmol/l
Dissolved CO ₂	0.5 to 30	mmol/l
pH	2 to 5	
pCO ₂	10 to 675	mmHg

6. A multiple compartment flexible bag assembly according to claim 5, in which the concentration of dissolved carbon dioxide is from 5 to 15 mmol/l.

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7. A multiple compartment flexible bag assembly according to claim 1, in which said second predetermined volume of the aqueous acid component solution is intended for admixture with said first predetermined volume of the bicarbonate component solution in the preparation of a peritoneal dialysis fluid and in which the formulation of said aqueous acid component solution comprises the following electrolytes, glucose, acid and dissolved carbon dioxide at the limits or within the range of concentrations, pH and pCO₂ values as follows:

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Sodium	0 to 400	mmol/l
Potassium	0 to 5	mmol/l
Calcium	0 to 17.5	mmol/l

Magnesium	0 to 7.5	mmol/l
Chloride	0 to 500	mmol/l
Glucose	0 to 3000	mmol/l
Acid	0 to 100	mmol/l
Dissolved CO ₂	0.5 to 30	mmol/l
pH	2 to 5	
pCO ₂	10 to 760	mmHg
Water		

8. A multiple compartment flexible bag assembly according to claim 7, in which the concentration of dissolved carbon dioxide is from 5 to 15 mmol/l.

5

9. A multiple compartment flexible bag assembly according to any one of the preceding claims, over-wrapped in a flexible gas-impermeable plastic material.

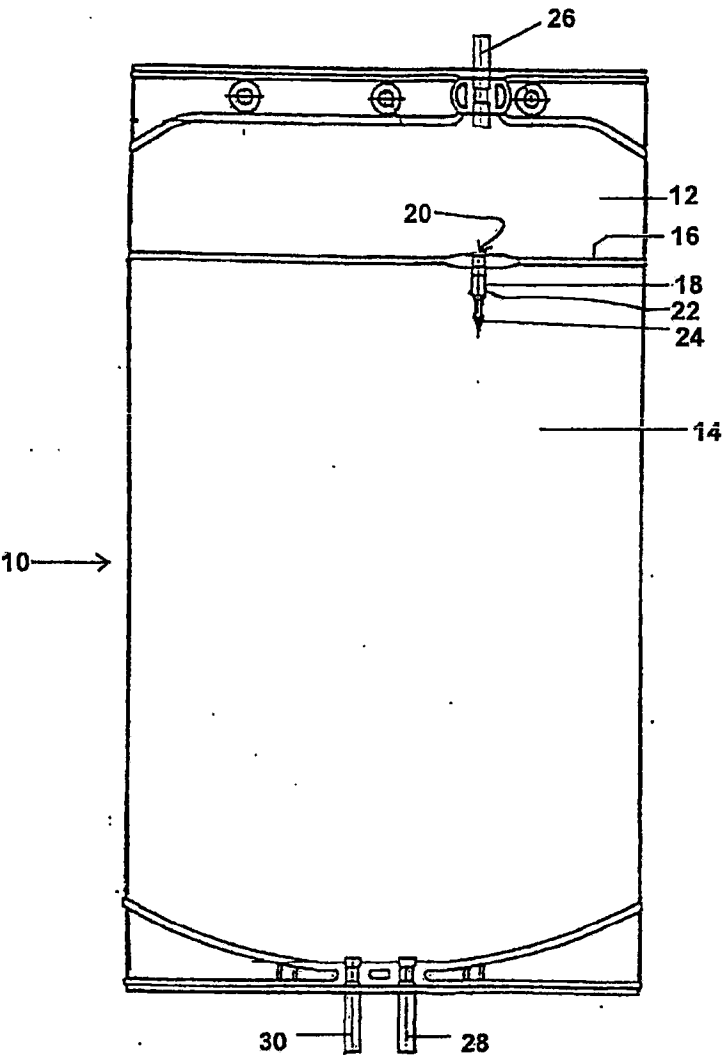
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10. A process for preparing an aqueous acid component solution to be contained in at least one compartment of a multiple compartment flexible bag assembly of any one of the preceding claims, which comprises the steps of determining the carbon dioxide partial pressure value exhibited by an aqueous bicarbonate component solution, preparing the aqueous acid component solution, and introducing carbon dioxide into the prepared aqueous acid component solution to obtain an aqueous acid component solution which exhibits a carbon dioxide partial pressure value which substantially matches said carbon dioxide partial pressure value determined for said aqueous bicarbonate component solution.

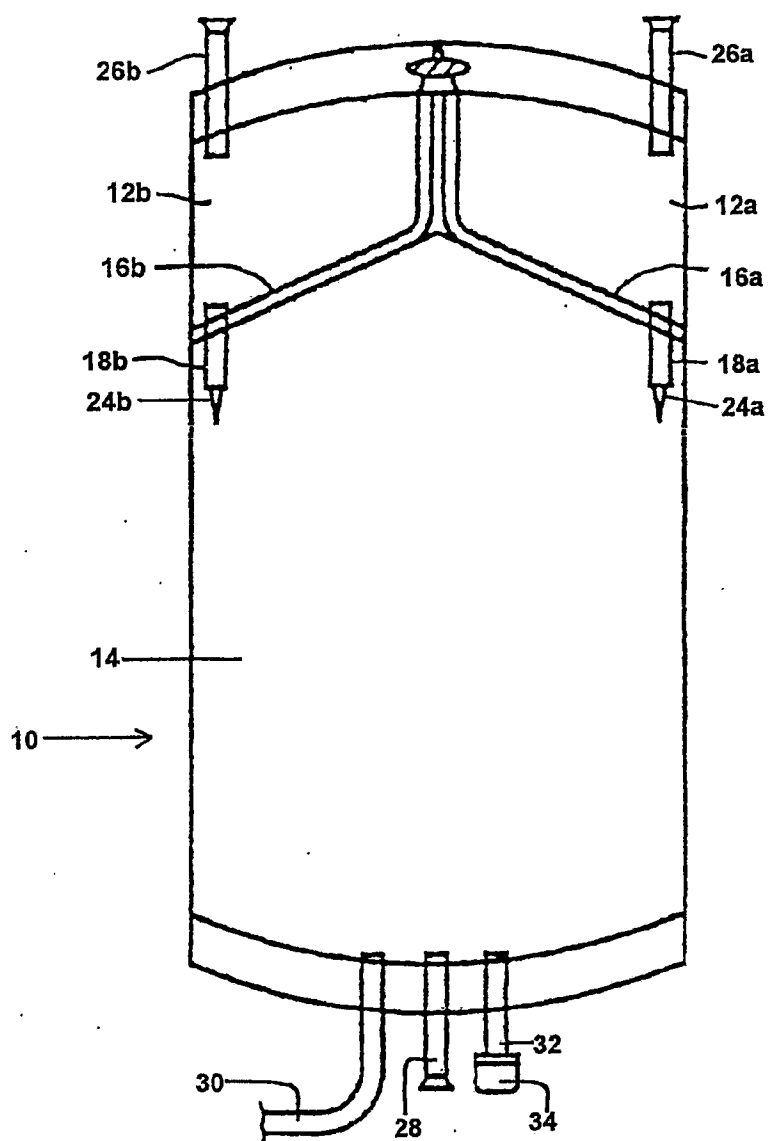
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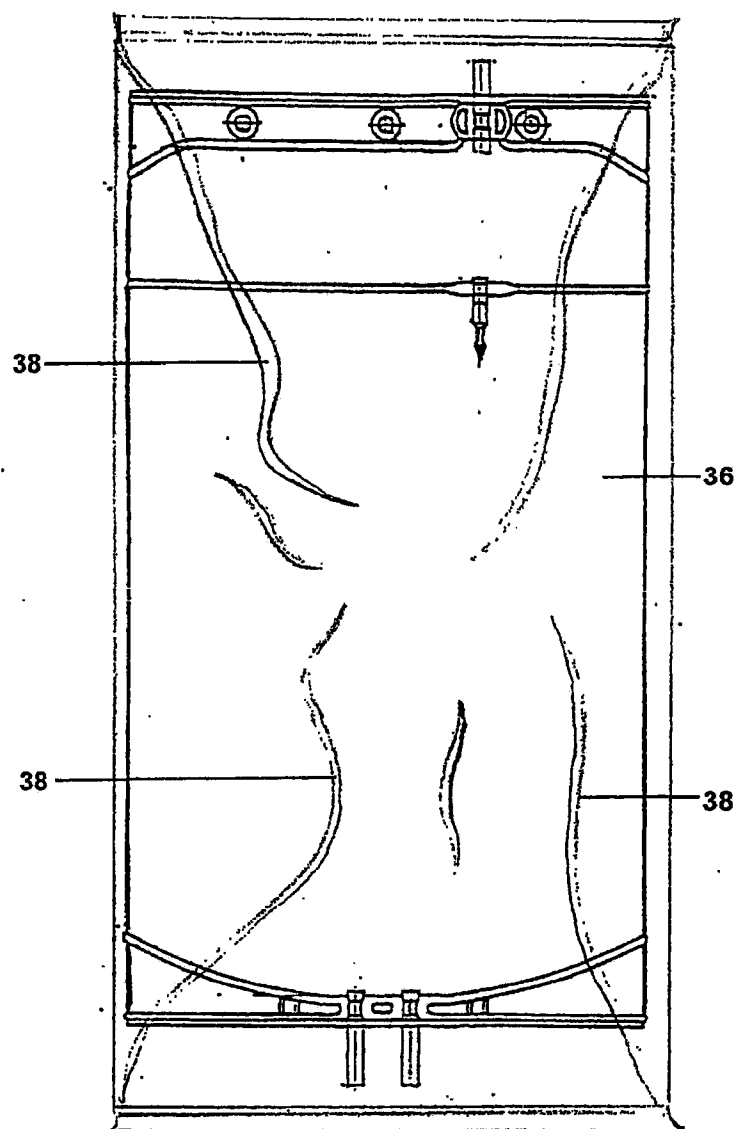
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- Figure 1 -

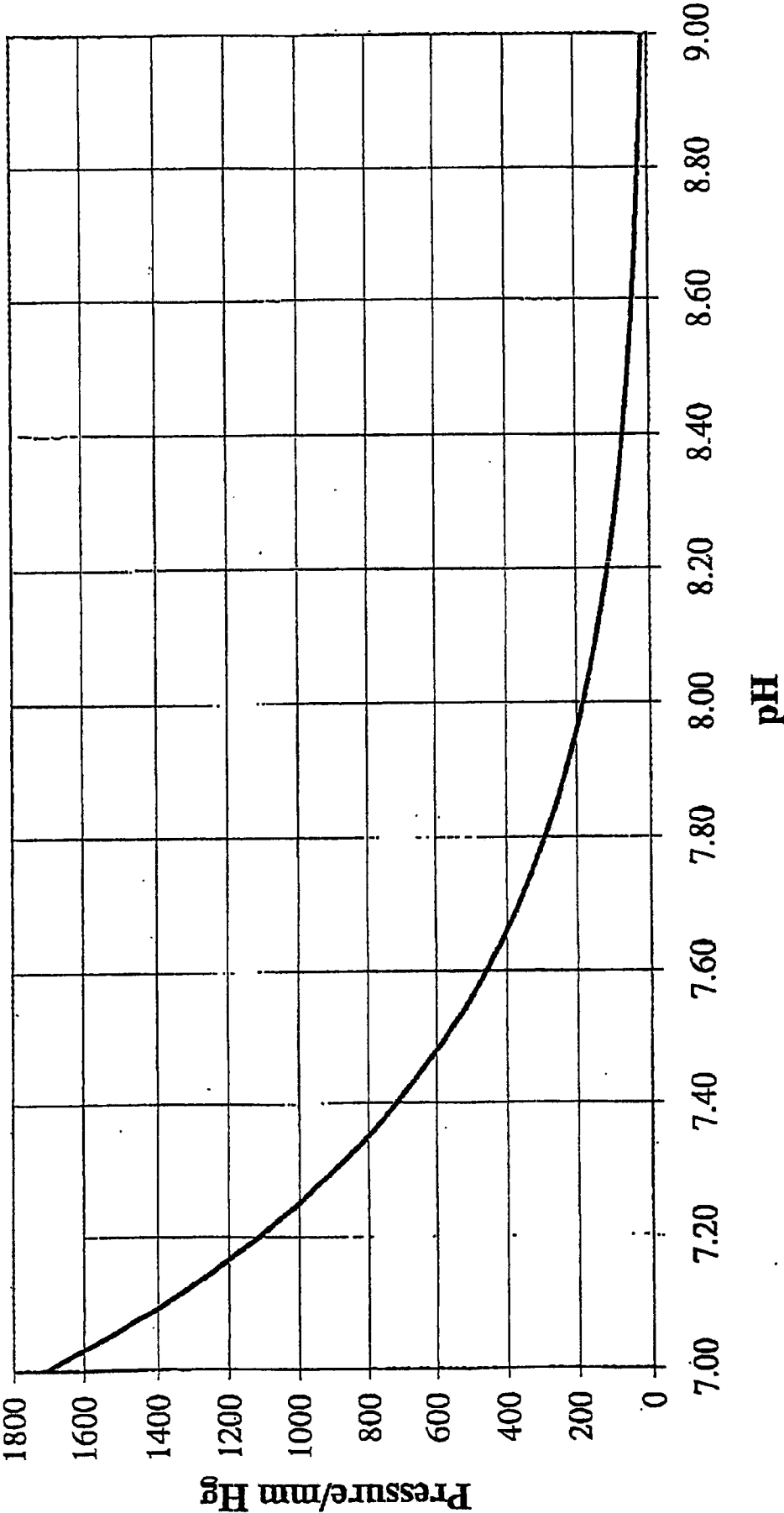


- Figure 2 -



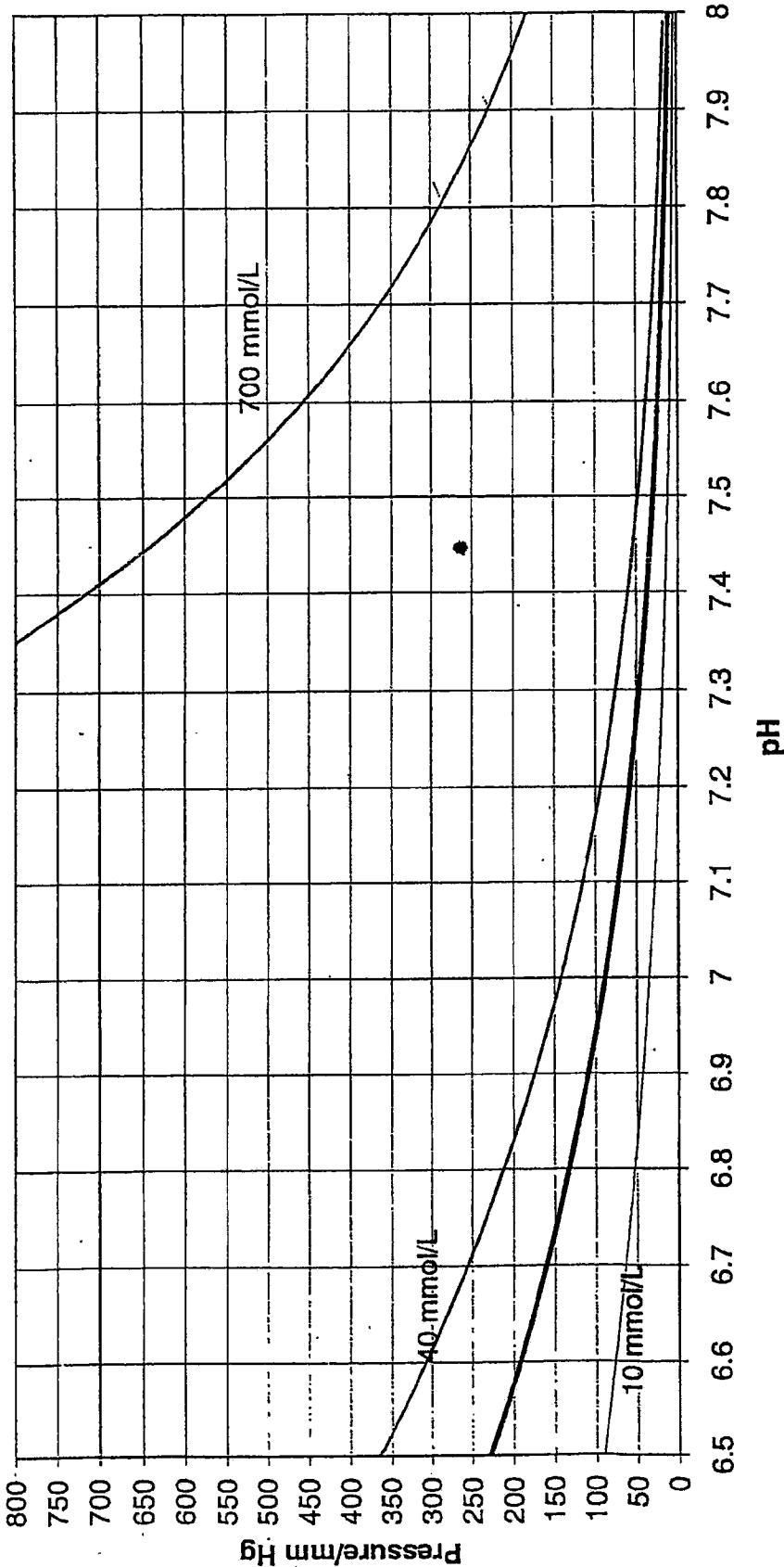
- Figure 3 -

Partial pressure of CO₂ vs. pH for fix TCO₂ = 700 mmol/L.

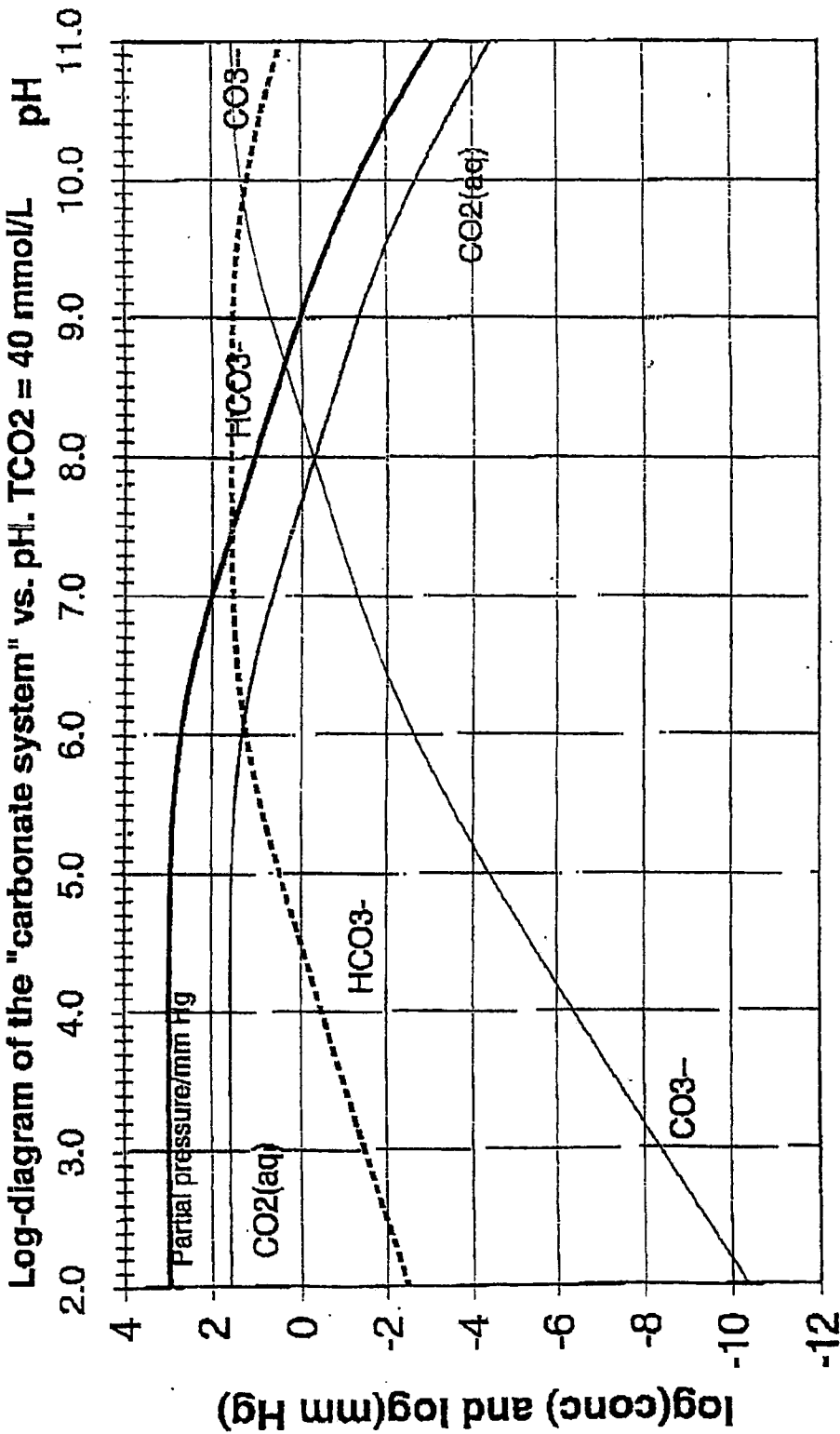


- Figure 4 -

Partial pressure of CO₂ vs. pH, at constant TCO₂. TCO₂ = 10, 25, 40 and 700 mmol/L



- Figure 5 -



- Figure 6 -

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/00183

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61M 1/14, A61J 1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61M, A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5200200 A (VEECH, R.L. ET AL), 6 April 1993 (06.04.93), column 7, line 64 - column 8, line 32, figure 1, abstract --	1-3,5-8
A	US 6309673 B1 (DUPONCHELLE, A. ET AL), 30 October 2001 (30.10.01), abstract --	1-10
A	US 4630727 A (FERIANI, M. ET AL), 23 December 1986 (23.12.86), column 6, abstract -- -----	1-10

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

30 April 2003

Date of mailing of the international search report

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Information on patent family members

International application No.

PCT/SE 03/00183

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
US	5200200	A	06/04/93	US	4929449 A	29/05/90
				CA	1285528 A	02/07/91
US	6309673	B1	30/10/01	AU	6384200 A	10/04/01
				CA	2352561 A	15/03/01
				CN	1336825 T	20/02/02
				EP	1131077 A	12/09/01
				US	6475529 B	05/11/02
				US	2002012707 A	31/01/02
				WO	0117534 A	15/03/01
US	4630727	A	23/12/86	AT	59774 T	15/01/91
				BR	8501579 A	03/12/85
				CA	1234784 A	05/04/88
				DE	3581227 D	00/00/00
				EP	0161471 A,B	21/11/85
				SE	0161471 T3	
				ES	542004 A	16/09/86
				ES	8700059 A	01/01/87
				IT	1214872 B	18/01/90
				IT	8485554 D	00/00/00
				JP	7041071 B	10/05/95
				JP	61000355 A	06/01/86